ORIGINAL ARTICLE

Factors associated with progression and outcomes of primary biliary cholangitis: A cohort study, 2010-2019

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Background: Primary biliary cholangitis (PBC) can impact both the quality of life and the survival of patients. The study aimed to determine the survival rate and associated variables in patients with PBC. **Materials and Methods:** This cohort research comprised 65 patients diagnosed with PBC who were admitted to the pathology section between January 2010 and December 2019. Survival was determined by reviewing hospital medical data and following up with the patients. The impact of demographic factors, clinical, laboratory, and histopathological aspects on patient survival time was investigated using Kaplan-Meier survival analysis and Cox regression. **Results:** The average period of follow-up was 6.25 years with a standard deviation of 3.2 years. In surviving patients, the baseline bilirubin level was 2.83, but in deceased or transplanted patients, it was 8.95 ($P = 0.002$). The baseline albumin level was 3.99 in surviving patients and 3.66 in deceased or transplanted patients ($P = 0.024$). The incidence of cirrhosis in those who survived was 1.8%, but in patients who died or underwent a transplant, it was 40%. Out of 65 cases, 3 patients (4.7%) died and 7 (10%) had liver transplants. Survival rates of patients vary based on factors such as jaundice ($P = 0.002$), weariness ($P = 0.03$), cirrhosis ($P < 0.001$), and vitiligo ($P = 0.033$). There were notable variations in the average Mayo score between the two groups of patients who had liver transplantation and survived, with scores of 7.21 and 5.61, respectively. **Conclusion:** The study found that aspartate aminotransferase and alanine aminotransferase levels, baseline and final bilirubin, albumin, antinuclear antibody, the presence of cirrhosis, and jaundice significantly influenced patient survival with PBC.

Key words: Cirrhosis, disease progression, primary biliary cholangitis, survival rate

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INTRODUCTION

Primary biliary cholangitis (PBC) is a rare condition that leads to the progression of chronic cholestatic liver diseases. It mainly impacts women in middle age and older and can advance to cirrhosis and liver failure.[1] The exact cause of the condition is unknown, but it seems that a combination of environmental and genetic variables is important in its development.[2]

Due to the increasing use of routine biochemical screening, more patients with PBC are being diagnosed even when they do not show symptoms. Several studies have shown that the survival rate of patients with PBC is lower compared to the general population, ranging from 7.5% to 16%. Specific clinical symptoms, liver enzyme level abnormalities, and histological characteristics can reliably predict the course of the illness.[3]

PBC commonly presents with pruritus (40%), tiredness (45%), and upper abdomen pain. However, over half of patients have no symptoms when diagnosed.[4] The condition can be identified by a combination of clinical and analytical approaches, as well as by examining liver samples. Moreover, having

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chronic liver disease for over 6 months, with blood alkaline phosphatase (ALP) levels at least 1.5 times the normal range, and anti-mitochondrial antibody (AMA) levels exceeding the normal range.[5] Having a liver biopsy is crucial for confirming the diagnosis. It is crucial to rule out other chronic liver problems such as persistent alcohol consumption, viral hepatitis, and metabolic liver illnesses during the initial diagnosis.

AMAs that target the E2 component of the pyruvate dehydrogenase complex are a very specific serological test for PBC. Moreover, the use of ursodeoxycholic acid has been demonstrated to improve liver function tests, histological features, and overall survival in individuals with PBC.[6,7]

Minnesota had the highest prevalence rate of PBC in 1995, with 40.2 cases per 100,000 people. An epidemiological study shows a recent 8% increase in the annual relative prevalence.[2] There has been no thorough epidemiological study done on individuals with this disease in Iran, resulting in a lack of knowledge about the current disease state in the country. Performing descriptive epidemiologic studies is essential for determining the prevalence of diseases and guiding resource distribution decisions. Moreover, these investigations provide a basis for further epidemiological study into the root causes of diseases, such as environmental or genetic factors. The study's objective is to identify individuals with the disease and monitor their progress by documenting their information in the liver disease registration system of the Gastroenterology Research Center at Isfahan University of Medical Sciences. Furthermore, it aims to collect preliminary data and the prognosis of this cohort of chronic liver patients. The study seeks to examine the future progression, current treatment methods, long-term remission rate, and incidence of liver cirrhosis in individuals with this condition in Isfahan.

MATERIALS AND METHODS

The study analyzed a retrospective cohort of patients diagnosed with "primary biliary cirrhosis" or "PBC" at Al Zahra Hospital, affiliated with Isfahan University of Medical Sciences, between January 1, 2010, and December 2019. Analyzed were medical profiles, encompassing patient demographics, and clinical features (ClinicalTrials.gov no.: 1399.330). We conducted a retrospective cohort analysis that comprised 65 consecutive patients with PBC. The criteria for inclusion consist of patients admitted to the hospital with elevated liver enzymes, individuals who have undergone a liver biopsy to confirm PBC, and those excluded for other conditions associated with high liver enzymes (such as viral hepatitis, Wilson's disease, drug-induced liver damage, gallstones, and tumors). Moreover, the lack of access to patients' information and insufficient cooperation from patients in providing information were considered exclusion criteria. The study's diagnostic criteria include clinical features suggesting a long-lasting cholestatic disorder, a significant increase in alkaline phosphatase levels, positive AMA status, and liver histology consistent with PBC, especially in patients with low or negative AMA titers.[1] This study utilized the census approach to include all eligible people diagnosed with PBC who were hospitalized during the given time frame.

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This study used the census approach to include all eligible patients diagnosed with PBC who were hospitalized during the given time frame.

The researcher used a methodical approach by accessing the hospital's medical records department to create a list of patients who were admitted with a diagnosis of PBC. The researcher collected relevant information by carefully reviewing the patients' files and, if needed, contacting the patients or their family members.

Demographic and clinical information including age, gender, disease duration, time of diagnosis, initial symptoms, coexisting medical conditions, laboratory, and pathology results will be collected from patient records and organized into a detailed checklist. Data collection was recorded. Furthermore, when reaching out to the patients, many factors such as hospitalization cases, disease recurrence, and treatment strategies were considered. Specific clinical data such as blood bilirubin levels, albumin levels, prothrombin time, the presence of edema, and diuretic drug status were meticulously examined and recorded to calculate the Mayo risk score.

After the diagnosis, the patients were observed for a period of time to evaluate the development of complications related to liver cirrhosis, including deterioration of ascites, encephalopathy, gastrointestinal bleeding, as well as liver transplantation, and mortality. Supplementary materials

included laboratory data, radiographic reports, and pathology reports.

Patients were continuously tracked from the time of diagnosis until the trial ended. Their condition was evaluated using mortality, liver transplantation, and survival without transplantation. The study also examined the overall survival rate and patient survival in connection with demographic and clinical parameters. The Mayo score was used to evaluate the severity of PBC. This criterion evaluates the factors of age, serum bilirubin level, aspartate aminotransferase (AST) level, variceal bleed, and albumin level.[8]

Statistical analysis

The standard error (SE) of the mean ± SE is utilized to represent data. The study utilized Chi-square analysis, Student's *t*-test, or Mann–Whitney test to compare patients based on their response status after 1 year.

We analyzed the Kaplan–Meier estimated survival rate without liver transplantation for the entire series and two response groups during all follow-up periods. The predicted survival for the first 9 years was obtained for each patient.

The Cox model was used to assess the univariate relationships between the predictive factors and death or liver transplantation. A cutoff point was established for each quantitative variable to separate the data into two classes, and relative risks were computed. A $P < 0.05$ was deemed statistically significant.

RESULTS

Sixty-five patients diagnosed with PBC hospitalized to Al Zahra Hospital in Isfahan during 2010 were included in this study. Al Zahra Hospital is a referral hospital for patients with PBC, who were continuously monitored during the trial period. The average length of follow-up was 6.25 years with a standard deviation of 3.2 years. The average age of patients at the time of diagnosis was 42.95 years with a standard deviation of 13.3. Out of the total, 49 patients (75.4%) were women and 16 patients (24.6%) were men. The average age of males was 41.88 ± 11.85 years and for females, it was 45.31 ± 16.81 years ($P = 0.37$). Seven patients (10.8%) underwent transplantation from the cases described. Out of the total sample, 4 patients (6.2%) were at Stage 1, 38 individuals (58.2%) were at Stage 2, 21 individuals (32.3%) were at Stage 3, and 2 individuals (3.1%) were at Stage 4 in terms of disease progression. Out of the patients diagnosed, 6 (9.2%) had no symptoms. Pruritus was the most common clinical symptom observed, present in 42 cases (64.6%). The incidence of the symptoms mentioned decreased significantly over the 9-year research period [Figure 1].

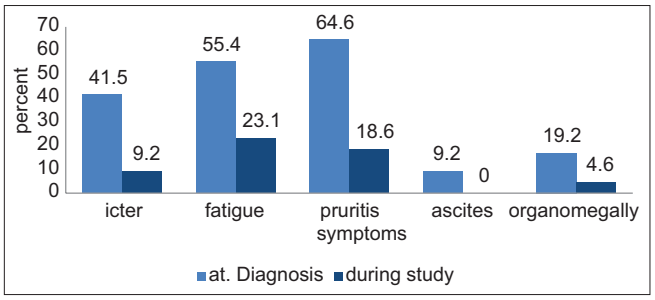

Figure 1: Percentage frequency of clinical symptoms at the time of diagnosis and at the time of study

The average Mayo score for the total research cohort was 5.89 ± 1.61, ranging from 3.29 to 10.64. Over the 9-year follow-up period, there was a significant decline in the levels of liver enzymes. The levels of bilirubin and alkaline phosphatase were 2.16 ± 0.37 ($P < 0.001$) and 499.6 ± 92.2 ($P < 0.001$), respectively, whereas AST levels were 94.9 ± 34.6 ($P < 0.001$). The alanine aminotransferase (ALT) level decreased by 107.1 ± 32.9 units with a significance of $P = 0.008$. During the 9-year research period, three patients died and seven underwent liver transplants. Significant variations were seen in the mean Mayo score, albumin level, and bilirubin level between the groups that received live and dead transplantations at the time of diagnosis and study [Table 1].

Analysis of histological features revealed that out of the 65 patients evaluated, 10 individuals (15.4%) exhibited interface hepatitis, 38 individuals (58.5%) had lymphocyte infiltrate, and 42 individuals (64.6%) had destructive cholangitis. Five individuals (7.7%) exhibited histopathological signs of cirrhosis. Regarding comorbidities, 3.1% of individuals had rheumatoid arthritis, 7.7% had diabetes, 12.3% had vitiligo, and 9.2% had inflammatory bowel disease. The study found substantial differences in the occurrence of icterus and weariness at the time of diagnosis, ascites, lymphocyte infiltration, and cirrhosis between the living and dead transplantation groups.

The mean survival time of the patients was 9.56 years with a standard deviation of 0.42 years. The survival rates for patients at 1 year, 2 years, 5 years, and 10 years were 93.8%, 90.8%, 87.7%, and 74.6%, respectively [Figure 2].

Table 2 displays the mean survival duration of patients based on demographic and clinical factors. The survival rates of patients vary significantly based on the existence of jaundice, fatigue, cirrhosis, and vitiligo at the time of diagnosis, as indicated by the logarithmic rank test ($P = 0.002$, $P = 0.03$, $P < 0.001$, and $P = 0.033$, respectively).

The Cox regression analysis showed that AST, ALT, final bilirubin levels, antinuclear antibody (ANA) levels, albumin

Table 1: Compare demographics and lab data between surviving and death transplant groups

Variables	Patients status		Normal range	*P*
	Alive	Death or transplant		
Patients age (year)	49.38±12.7	49.8±17.1		0.93
Female, n (%)	49 (75)	16 (25)		0.06
Mayo risk score	5.61±1.38	7.21±2.15		0.003
AST at diagnosis	146.16±39.69	114.6±30.78	(normal <30 IU/L)	0.73
AST last result	40.98±27.50	64.9±27.9	(normal <30 IU/L)	0.092
ALT at diagnosis	166.06±39.76	110.2±67.4	(normal <28 IU/L)	0.54
ALT last result	44.9±28.6	67.10±27.7	(normal <30 IU/L)	0.15
ALK at diagnosis	978.3±197.8	897.0±511.2	(normal <270 IU/L)	0.64
ALK last result	466.5±296.5	609.3±320.5	(normal <270 IU/L)	0.34
Bilirubin at diagnosis	2.83±2.41	8.95±7.67	(normal <1.2 mg/dL)	<0.001
Bilirubin last result	1.15±0.82	4.90±2.66	(normal <1.2 mg/dL)	0.003
AMA	39.97±8.63	31.88±26.14	Near zero	0.75
ANA	2.67±2.29	2.11±1.46	<5	0.52
PT	12.14±1.86	12.9±2.81	<13	0.29
INR	1.21±0.03	1.29±0.28	<1.2	0.29
Albumin	3.99±0.35	3.66±0.7	(normal 3.8–4.2 mg/dL)	0.031

AST=Aspartate aminotransferase; ALT=Alanine aminotransferase; ALP=Alkaline phosphatase; AMA=Anti-mitochondrial antibody; PT=Prothrombine time; ANA=Antinuclear antibodies; INR=International normalized ratio

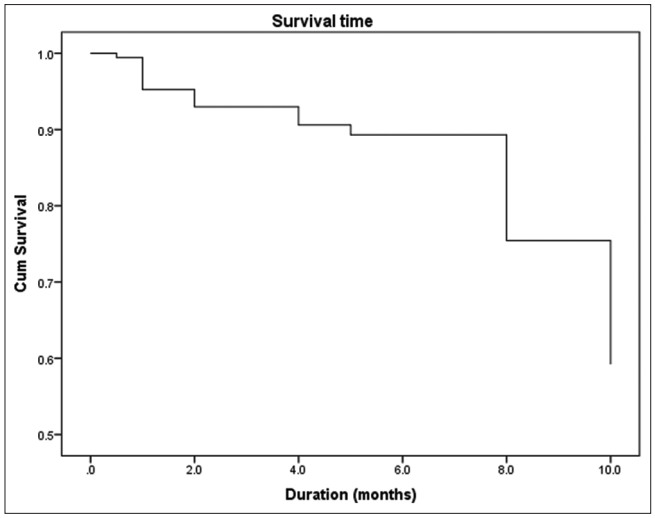

Figure 2: Observed survival to death or liver transplantation for the primary biliary cholangitis patients

levels, changes in bilirubin levels, cirrhosis, and jaundice significantly affected the survival of patients [Table 3].

DISCUSSION

PBC plays a major role in developing long-lasting cholestatic liver conditions. It is important because it can cause serious damage to liver tissue, namely resulting in cirrhosis and liver failure. Therefore, it is crucial to closely observe patients and use suitable treatment protocols. Insufficient therapy leads to the condition progressing and, in some cases, causing death due to liver damage.[8]

Although the exact cause of the disease is unknown, studies have shown that a combination of environmental and genetic variables plays a role in the development and advancement of this condition.[1] This study aimed to identify clinical changes and laboratory data in patients with PBC.

The examination of the patients in the study showed that the mortality or requirement for transplantation rate was 15.4%. Demographic characteristics such as age, gender, and age at disease diagnosis did not have a significant impact on death. The condition was notably more common among women, with a prevalence of 75.4%. A study in Europe revealed that the prevalence of PBC in women was 5.5 times greater than in men.[9] Poupon *et al*. discovered that the mortality rate associated with PBC was higher in men than in women.[10] Toy *et al*. documented a yearly cumulative mortality rate of 1.9% in individuals with PBC.[11]

Significant variations were seen in the mean Mayo score, bilirubin level at diagnosis and at the time of study, and albumin level between the groups of patients who underwent liver transplantation and lived, and those who did not survive. Kim *et al*.'s study concluded that the Mayo score is a dependable predictor of mortality due to PBC.[12] Lammers *et al*.'s work introduced the Mayo score as a reliable tool for evaluating the prognosis of PBC disease.[12] Lammers *et al*. conducted a study that revealed significantly higher levels of bilirubin and alkaline phosphatase in persons with PBC compared to the normal range.[5,13]

The study found that certain clinical signs such as jaundice, fatigue, ascites, lymphocyte infiltration, and cirrhosis were significantly related to patient death upon diagnosis. The prevalence of these symptoms was higher in deceased transplant patients, consistent with the results of Goode

Table 2: Duration of patient survival based on study variables

Variables	Patients status		
	Alive, *n* (%)	Death or transplant, *n* (%)	*P*
Age (year)			
<50	32 (84.2)	6 (60)	0.99
≥50	23 (41.8)	4 (40)	
Sex			
Female	42 (76.4)	7 (70)	0.698
Male	13 (23.6)	3 (30)	
Age diagnosis			
<50	40 (72.7)	6 (60)	0.99
≥50	15 (27.3)	4 (40)	
Icter at diagnosis			
No	37 (67.3)	1 (10)	0.001
Yes	18 (32.7)	9 (90)	
Fatigue at diagnosis			
No	28 (50.9)	1 (10)	0.034
Yes	27 (49.1)	9 (90)	
Pruritis at diagnosis			
No	22 (40)	1 (10)	0.084
Yes	33 (60)	9 (90)	
Ascites at diagnosis			
No	52 (94.5)	7 (70)	0.042
Yes	3 (5.5)	3 (30)	
Organomegaly at diagnosis			
No	48 (87.3)	6 (60)	0.057
Yes	7 (12.7)	4 (40)	
Interface hepatitis			
No	47 (85.5)	8 (80)	0.65
Yes	8 (14.5)	2 (20)	
Lymphocyre infiltrate			
No	26 (47.3)	1 (10)	0.037
Yes	29 (52.7)	9 (90)	
Destruct chollangitis			
No	19 (34.5)	4 (40)	0.73
Yes	36 (65.5)	6 (60)	
Cirrhosis			
No	54 (98.2)	6 (60)	<0.001
Yes	1 (1.8)	4 (40)	
Bridge fibrosis			
No	16 (29.1)	3 (30)	0.99
Yes	39 (70.9)	7 (70)	
Thyroid			
No	45 (81.8)	7 (70)	0.41
Yes	10 (18.2)	3 (10)	
Rheumatoid arthritis			
No	53 (96.4)	10 (100)	0.99
Yes	2 (3.6)	0	
Diabetes			
No	51 (92.7)	9 (90)	0.58
Yes	4 (7.3)	1 (10)	
Vitiligo			
No	50 (90.9)	7 (70)	0.098
Yes	5 (9.1)	3 (30)	
IBD			
No	50 (90.9)	9 (90)	0.99
Yes	5 (9.1)	1 (10)	
AIH			
No	53 (96.4)	10 (100)	0.99
Yes	2 (3.6)	0	
Autoimmune disorders			
No	34 (61.8)	5 (50)	0.504
Yes	21 (38.2)	5 (50)	
Overall comorbidity			
No	34 (61.8)	5 (50)	0.504
Yes	21 (38.2)	5 (50)	
Icteric at the beginning of study			
No	51 (92.7)	8 (80)	0.23
Yes	4 (7.3)	2 (20)	
Fatigue at the beginning study			
No	44 (80)	6 (60)	0.22
Yes	11 (20)	4 (40)	
Organomegaly at the start of the study			
No	54 (98.2)	8 (80)	0.059
Yes	1 (1.8)	2 (20)	
Pruritis at the start of the study			
No	44 (80)	9 (90)	0.67
Yes	11 (20)	1 (10)	
Ascites start of the study			
No	55 (100)	10 (100)	0.9
Yes	0	0	
Stage			
1	4 (7.3)	0	0.28
2	34 (61.8)	4 (40)	
3	15 (27.3)	6 (60)	
4	2 (3.6)	0	
Mayo risk score			
≤6	52 (9.1)	5 (35)	0.99
>6	16 (90.9)	9 (65)	

AIH=Autoimmune hepatitis; IBD=Inflammatory bowel disease

et al.'s study.[14] Montano-Loza *et al*. found that individuals who died from PBC had a greater incidence of clinical symptoms such as jaundice and ascites.[15] Vierling conducted a study that revealed a significant association between the presence of ascites and patient death in cases of PBC.[16] Research by Jones *et al*. revealed that fatigue symptoms were significantly more common in deceased transplantation PBC patients than in surviving individuals.[17]

The study found that patients had an average overall survival rate of 9.56 ± 0.42 years. The survival rates at 1 year, 2 years, 5 years, and 10 years were 93.8%, 90.8%, 87.7%, and 84.6%, respectively. Moreover, there was a significant difference

Table 3: Hazard ratio and univariate analysis of prognostic factors for mortality or transplantation in long-term follow-up

Variable	Survival status (*n*=65)		Crude hazard ratio (95% CI)	*P*
	Alive (*n*=55; 85%), *n* (%)	Died/transplanted (*n*=10; 15%), *n* (%)		
Patients age (year)				
Mean	49.38±12.7	49.8±17.1	1.07 (0.008–144)	0.98
<50	32 (58.2)	6 (60)	Reference	
≥50	23 (41.8)	4 (40)	0.89 (0.251–3.17)	0.86
Diagnostic age (year)				
Mean	42.91±12.76	43.20±16.84	99 (0.95–1.05)	0.98
<50	40 (72.7)	6 (60)		-
≥50	15 (27.3)	4 (40)	1.81 (0.51–6.5)	0.36
Sex (female)	42 (76.4)	70 (7)	1.28 (0.33–4.96)	0.72
AST baseline (U/L)	146.16±39.7	114.6±30.8	0.99 (0.99–1.004)	0.82
Final AST (U/L)	40.98±27.5	64.9±78.7	1.01 (1.001–1.023)	0.033
AST mean changes (%)	−50.2±28.9	−7.2±37.3	1.01 (0.99–1.04)	0.22
ALT baseline (U/L)	166.1±39.8	110.2±21.3	0.99 (0.99–1.005)	0.54
ALT final (U/L)	44.9±28.6	67.1±27.7	1.1 (1–1.13)	0.046
ALT mean changes (%)	−50±32.6	−5.6±42.3	1.004 (0.99–1.02)	0.62
Baseline ALK (U/L)	978.3±197.8	897.0±511.2	0.99 (0.99–1.001)	0.48
Final ALK (U/L)	446.5±296.5	609.3±296.5	1.001 (1–1.002)	0.12
ALK mean changes (%)	−45.3±7.01	−5.7±53.3	1.003 (0.99–1.01)	0.53
Bilirubin baseline (mg/dL)	2.83±0.34	8.95±2.43	1.28 (1.09–1.50)	0.002
Bilirubin final (mg/dL)	1.15±0.82	4.9±2.7	0.94 (0.82–1.08)	0.38
Bilirubin mean changes (%)	−49.4±23.3	−57.9±32.4	0.96 (0.93–0.99)	0.029
AMA	39.97±8.62	31.88±26.14	0.99 (0.96–1.02)	0.45
ANA	2.67±2.29	2.11±1.46	0.22 (0.051–0.97)	0.045
Pt	12.14±1.86	12.9±2.81	0.80 (0.56–1.15)	0.22
INR	1.21±0.28	1.29±0.28	0.81 (0.56–1.56)	0.24
Albumin	3.99±0.35	3.66±0.70	0.14 (0.26–0.77)	0.024
Interface hepatitis (yes)	8 (14.5)	2 (20)	1.45 (0.31–6.8)	0.64
Lymphocyte infiltrate (yes)	29 (47.3)	9 (90)	5.79 (0.72–46.8)	0.1
Destructive cholangitis (yes)	36 (65.5)	6 (60)	0.91 (0.25–3.3)	0.88
Cirrhosis (yes)	1 (1.8)	4 (40)	9.63 (2.46–37.6)	0.001
Bridge fibrosis (yes)	39 (70.9)	7 (70)	2.07 (0.48–8.79)	0.33
asymptomatic (yes)	6 (10.9)	0	23.3 (0.001–84.8)	0.56
Icter (yes)	18 (32.7)	9 (90)	8.91 (1.88–89.9)	0.04
Fatigue (yes)	27 (49.1)	9 (90)	3.47 (0.39–31.3)	0.27
Pruritus (yes)	33 (60)	9 (90)	0.84 (0.08–5.5)	0.88
Ascites (yes)	3 (5.5)	3 (30)	1.11 (0.14–9.1)	0.92
Organomegaly (yes)	7 (12.7)	4 (40)	1.13 (1.69–7.47)	0.91
Comorbidity (yes)	21 (38.2)	5 (50)	1.65 (0.48–5.72)	0.73
Mayo risk score	5.61±1.38	7.21±2.15	1.45 (1.09–1.95)	0.012

AST=Aspartate aminotransferase; ALT=Alanine aminotransferase; AMA=Anti-mitochondrial antibody; PT=Prothrombine time; ANA=Antinuclear antibodies; ALK=Anaplastic lymphoma kinase; INR=International normalized ratio; CI=Confidence interval

in the survival rates of patients depending on whether they had ascites, organomegaly, or itching at the time of diagnosis ($P = 0.013$). Patients displaying these symptoms had a reduced average survival rate. Lammers *et al.*'s investigation revealed a significant association between the survival rate of individuals with PBC and the presence of ascites. Individuals with ascites had a decreased average survival rate of 15. Tomiyama *et al*. conducted a study that revealed a significant influence of serum albumin and bilirubin levels on patient survival.[18] Several studies have shown that numerous factors have a significant impact on patient survival. The determinants include the amount of liver enzymes and the appearance of early symptoms such as jaundice and itching in the early stages of the disease. Managing the above causes could perhaps control these symptoms. Survival rates of patients with PBC can be enhanced to some extent. Considering the limitations of this study, such as the small sample size and short follow-up period, it is necessary to conduct more research in this field simultaneously.

Study limitation

The study faced limitations such as a small sample size and short follow-up period, so it is suggested that more studies be done in this field.

CONCLUSION

The study found that patients with PBC had an average survival duration of 9.56 ± 0.42 years, with survival rates of 93.8% at 1 year, 90.8% at 2 years, 87.7% at 5 years, and 84.6% at 10 years. AST and ALT levels, baseline and final bilirubin, albumin, ANA, the presence of cirrhosis, and jaundice significantly influenced patient survival.

Author's Contribution

BT: Study idea, study design, interpretation and contribution in writing the paper. SMJS: Contributed in data collection and data analysis and preparation of paper. MHS: Contributed in data collection and data analysis. AB: Contributed in interpretation data and writing the analysis reports.

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Conflicts of interest

There are no conflicts of interest.

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